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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/446,235	12/04/89	BRAKEL C	EN247

EXAMINER
KUNZ, G

ART UNIT	PAPER NUMBER
1803	12

DATE MAILED: 06/05/92

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 2/28/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-51 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-51 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

This communication is a response to applicant's Amendment B filed February 28, 1992. Amendment B is a timely response to the first Office action on the merits mailed August 26, 1991 (Paper No. 8).

Claims 1 - 51 are pending in the case.

Claims 1 - 2, 4, 8, 12 - 14, 19, and 42 - 50 are rejected under 35 U.S.C. 102(b) as anticipated by Miller et al. (Biochimie 67: 769 -776, 1985). Miller et al. discloses modified oligonucleotide compounds that fall within the definitions of the claimed compounds and a method for inhibiting the function of an RNA. Figure 4 on page 773 shows several specific oligonucleotides possessing methylphosphonate linkages that fully meet the applicant's claimed compounds.

The applicant argues against this rejection on the basis that Miller et al. discloses exclusively oligomers in which all of the linkages are phosphonates and that these compounds fail to possess the additional criteria of the applicant that they create a RNAse sensitive duplexes with RNA. This argument is not deemed persuasive because the rejected claims are not limited by the functional language concerning the generation of an RNAse sensitive hybrid with RNA. Consequently, this rejection stands.

Claims 1 - 4, 12 - 14, and 42 - 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Stein et al. (Nucl. Acids. Res. 16(8): 3209 - 3221, 1988). Stein et al. discloses modified

oligomers with phosphorothioate linkages (see S-ODN-4 in Table 3, page 3216; this is an oligomer with phosphorothioate inter-nucleotide linkages). Such oligomers are resistant to nuclease digestion and were able to inhibit the functioning of RNA by creating RNAse sensitive duplexes (page 3220, last paragraph). The applicant argues that these modified oligomers containing phosphorothioate linkages do not anticipate the claimed compounds because they are not capable of hybridizing to a target RNA and that no mention is made in the reference of the sensitivity of the RNA-DNA duplex to RNAse. This argument has been fully considered but is not deemed persuasive because 1) the rejected claims are not limited to target RNA nor RNAse sensitive duplexes and 2) Stein et al. specifically notes that the RNA-DNA hybrids in which the DNA possesses phosphorothioate linkages are more sensitive to RNAse digestion than regular RNA-DNA duplexes (page 3320, last paragraph).

Claims 1 - 51 are rejected under 35 U.S.C. 103 as being unpatentable over Walder et al. (PNAS 85: 5011 - 5015, 1988) in view of Miller et al. (4,469,863) and Inoue et al. (Nucl. Acids Symposium Series, 18: 958 - 976, 1988).

Walder et al. discloses that the most important element in the efficacy of antisense oligomers inhibiting mRNA expression is the formation of a RNAse sensitive RNA-DNA duplex that is cleaved by the enzyme: "An important corollary of our results is that such modified analogs must not only retain normal

hybridization properties but should also form substrates that are recognized and cleaved by RNAse H (page 5015, second column, second paragraph).

Miller et al. discloses antisense oligomers with all methylphosphonate internucleotide linkages. These modified oligomers possess resistance to nucleases, can pass through the membranes of mammalian cells, and can form stable duplexes with complementary mRNA (page 769, "Summary").

Inoue et al. teaches that a span as small as three contigous phosphodiester linkages flanked by modified nucleotides (2'-O-methyl) was capable of forming an RNAse H-sensitive substrate (page 222, first paragraph).

The claimed modified oligonucleotides possess three primary characteristics: 1) endo- and exonuclease resistance, 2) ability to hybridize to its RNA complementary sequence, and 3) the ability to form a RNAse sensitive RNA-DNA duplex.

The person of ordinary skill in the art with the above references before him would have found the claimed modified oligomers obvious because of the necessity to have reduced the number of methylphosphonate internucleotide bonds in the oligomer in order to make the RNA-DNA duplex RNAse sensitive as Walder et al. emphasizes is critical to the efficacy of antisense oligonucleotides in inhibiting the express of mRNA.

The claimed methods of inhibiting the function of an RNA by contacting said RNA with a nuclease resistant antisense

oligomer that forms RNAse H sensitive duplexes with said RNA would also have been obvious in view of the above references that, as a whole, teach the same method.

Finally, the method for identifying modified antisense oligomers possessing the combination of nuclease resistance and the ability to form an RNase H substrate with complexes of RNA using gel electrophoresis instead of the release of acid soluble radioactivity as taught by Walder et al. (page 5012, "RNase H Assay") would also have been obvious to the person of ordinary skill in the art. The use of gel electrophoresis is a fundamental tool in molecular biology for separating different types of polynucleotides whether by size or by other physical properties such as single-stranded versus double-stranded forms, linear versus circular forms, etc.

The applicant's basic invention is the antisense oligomer with only a portion of the internucleotide linkages or bases modified in order to make the oligomer nuclease resistant. However, the prior art clearly teaches the necessity of combining both nuclease resistance with the ability to form RNase H sensitive duplexes with RNA. The applicant's gel assay is only one way to assay for RNase H sensitivity as Walder et al. substantiates.

Applicant's arguments against the obviousness rejection is moot in view of the prior art.

Claims 1 - 51 rejected under 35 U.S.C. § 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The critical issue in this rejection is that the applicant is attempting to define his invention primarily with functional language. This is inappropriate because the state of art of nucleic acid chemistry is well developed and thus allows compounds to be defined in specific structural terms. Without such specificity, it is practically impossible for the examiner to search the claims and equally difficult for the person of ordinary skill in the art to understand the metes and bounds of the invention.

The applicant's arguments against each of the rejections under 35 U.S.C. 112, second paragraph, amounts to his stating that the law does not require greater specificity and that the claims are clear in view of the specifications. The examiner holds the opposite point of view for the reasons already of record on pages 5 - 8 of the first Office action on the merits mailed August 26, 1991 (Paper No. 8).

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz whose telephone number is (703) 308-3995.

Gary L. Kunz:glk
May 31, 1992

Johnnie R. Brown
JOHNNIE R. BROWN
SUPERVISORY PATENT EXAMINER
ART UNIT 183